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09/478,668	01/06/2000	GARY A. BANNON	HS-102-DIV	1978

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EXAMINER
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ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/18/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/478,668	BANNON ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 37-59 are pending.

2. The following new grounds of rejections are necessitated by the amendment filed 9/21/01.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 37-51 and 53-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a modified allergen from peanut consisting of IgE binding epitopes from Ara h1, Ara h2 and Ara h3 (See page 26-27) wherein the IgE binding site (epitope) has at least one amino acid residues changes to alanine or methionine by amino acid substitution (See page 24, line16-18; page 28, line 6-9), the resulting modified allergen Ara h1 or Ara h2 binds less IgE than unmodified recombinant allergen, and only the modified allergen Ara h2 has been shown to bind similar amount of IgG and to stimulate T cell proliferation (page 28), does not reasonably provide enablement for (1) *any* modified protein allergen whose amino acid sequence is substantially identical to that of a natural protein allergen except that about 10 to 17% of the amino acids have been modified in at least one IgE epitope so that IgE biding to the modified protein allergen is reduced as compared with IgE binding to the natural protein allergen, the at least one IgE epitope being one that is recognized when the natural protein allergen is contacted with serum IgE from an individual that is allergic to the natural protein allergen, (2) *any* modified protein allergen wherein about 10 to 17% of the amino acids have been modified in all the IgE epitope of the natural protein allergen, (3) *any* modified protein allergen wherein at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to any natural protein allergen, (4) *any* modified protein allergen wherein at least one modified amino acid is located within a central portion of the at lest one IgE epitope, the central portion including about 40% of the amino acids of the at least one IgE epitope, (5) *any* modified protein allergen wherein at least one amino acid in the at least one IgE epitope of any natural protein allergen has been modified by substitution, (6) *any* modified protein allergen wherein at least one hydrophobic

amino acid in the at least one IgE epitope of the natural protein allergen has been substituted by a neutral or hydrophilic amino acid, (7) *any* modified protein allergen retains the ability to activate T cells, (8) *any* modified protein allergen retains the ability to bind IgG, (9) *any* modified protein allergen retains the ability to initiate a Th1-type response, (10) *any* modified protein allergen is *any* portion of the natural protein allergen, (11) *any* combination of *any* modified protein allergen and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ, and immune stimulatory oligodeoxynucleotide sequence containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response, (12) *any* modified protein allergen is made in transgenic plant or animal, (13) *any* modified protein allergen expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells, (14) *any* modified protein allergen wherein the natural protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes, (15) *any* modified protein allergen made by the process of claim 53, (16) *any* combination comprising any natural protein allergen and any masking compound wherein the masking compound being covalently or non-covalently bound to at least one IgE epitope of any natural protein allergen in such as a way that IgE binding is reduced as compared with IgE binding to the natural protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen, (17) *any* combination wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the natural protein allergen, (18) *any* combination wherein the masking compound is *any* antibody that binds non-covalently to the least one IgE epitope, (19) *any* combination retains the ability to activate T cells, (20) *any* combination retains the ability to bind IgG, and (21) any combination retains the ability to initiate a Th1-type response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working

examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification as filed discloses only modified allergens from peanut consisting of IgE binding epitopes from Ara h1 (SEQ ID NO: 2), Ara h2 (SEQ ID NO: 4) and Ara h3 (SEQ ID NO: 6) depicted in Figs 1-3. The amino acids that are critical for IgE binding of Ara h1, Ara h2 and Ara h3 are listed in Table 4, 5 and 6, respectively (See page 26-27). The specification also discloses that a single amino acid substitution by changing amino acid to alanine or glycine within the IgE binding epitope of Ara h1 (See page 24, line 16-18) leads to a reduced IgE binding whereas substituting alanine for arginine of Ara h1 lead to an increased IgE binding (See page 24, line 26-28). Likewise, a single amino acid within the IgE binding epitope of Ara h2 (Table 5) and Ara h3 (Table 6) would decrease IgE binding. The modified Ara h2 not only binds less serum IgE than the wild type but also binds similar amounts of IgG (See page 28, line 14-15; Fig. 4B) using serum from patients sensitive to peanut allergens. The specification further discloses that the modified Ara h2 retains the ability to stimulate T cell proliferation as measured by tritiated thymidine incorporation and the modified Ara h2 elicits a smaller wheal and flare in skin prick tests of a peanut sensitive individual (page 29).

Besides the specific modified peanut Ara h1, Ara h2, Ara h3 allergens mentioned above, the specification fails to provide *any* guidance as how to make and use *any* modified protein mentioned above that after amino acid substitution would retain the ability to activate T cells, bind IgG and initiate a Th-1 type response for treating any allergy. Furthermore, the specification fails to provide guidance and working examples of how to use a combination of any natural protein allergen and masking compound being covalently or non-covalently bound to at least one IgE epitope of any natural protein allergen. The specification fails to provide guidance as to which amino acids within the IgE binding epitopes of *any* natural protein allergens other than Ara h1, Ara h2 and Ara h3 are critical for IgE binding and which amino acid residues can be modified, in turn, would decrease IgE binding, maintain IgG binding and increase T cell proliferation and initiate a Th1-type response. The claims encompasses indefinite number of undisclosed modified protein allergen whose amino acid sequence is substantially identical to that of any natural protein allergen except that about 10 to 17% of the amino acids have been

modified in at least one IgE epitope so that that IgE binding is reduced compared to natural protein allergen.

There is no recognition in the art that sequence with identity predicts biological function. It is known in the art that even single amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. Fasler *et al.* (of record, PTO 892) teach that peptides derived from house dust mite Der p1 are modified by single amino acid substitutions at positions 173, 175, 176, 180 and 181 with alanine or glycine failed to induce Der p1 specific T cell proliferation and IL-2, IL-4 and IFN-γ production. Fasler *et al.* further teach that substituting a neutral amino acid residue such as Asn at position 173 with either a basic Lysine, which is a hydrophobic amino acid residue did not induce T cell proliferation and cytokine production. However, substitution amino acid positions other than 173, 175, 176, 180 and 181 induces normal or only slightly reduced proliferative responses and cytokine production by T cells (page 524, in particular). Burks *et al.* (of record, PTO 1449) teach a modified allergen from peanut Ara h1 where the immunodominant IgE binding epitope of Ara h1 is modified by amino acid substitution at position 1, 3, 4 and 17 with alanine or glycine reduced IgE binding. In contrast, substituting an alanine for glutamine residue at position 31 leads to an increase IgE binding. Burks *et al.* further teach that "there is no obvious position within each peptide that when mutated, would result in loss of IgE binding and there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 338, in particular). Stanley *et al* (of record, PTO 1449) teach a modified peanut allergen Ara h2 by amino acid substitution with alanine at position 67, 68 or 69 significantly reduced IgE binding while substitution of serine residue at position 70 leads to an increased in IgE binding. Stanley *et al* also teach that in general, "each epitope could be mutated to a non-IgE binding peptide by the substitution of an alanine for a single amino acid residue. However, there was no obvious position within each peptide that, when mutated, would result in loss of IgE binding. Furthermore, there was no consensus in the type of amino acid that, when changed to alanine, would lead to loss of IgE binding" (See page 251, in particular). Skolnick *et al* (of record, PTO 892) teach that sequence-based methods for function prediction are inadequate and knowing a protein's structure does not tell one its function (See abstract, in particular). Colman *et al* (of record, PTO 892) teach that a single amino acid changes within the interface of antibody-antigen complex can abolish the antibody-antigen interaction or binding entirely (See page 33, in particular).

With regard to a combination as recited in claims 54-59, given that the indefinite number of undisclosed modified protein allergen, it follows that any combination of any undisclosed modified protein allergen is not enabled.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

5. Claims 37-51 and 53-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification discloses only modified allergen from peanut consisting of IgE binding epitopes from Ara h1, Ara h2 and Ara h3 (See page 26-27) wherein the IgE binding site (epitope) has at least one amino acid residues changes to alanine or methionine by amino acid substitution (See page 24, line16-18; page 28, line 6-9), the resulting modified allergen Ara h1 or Ara h2 binds less IgE than unmodified recombinant allergen, and only the modified allergen Ara h2 has been shown to bind similar amount of IgG and to stimulate T cell proliferation (page 28).

The specification does not reasonably provide a **written description** of (1) *any* modified protein allergen whose amino acid sequence is substantially identical to that of a natural protein allergen except that about 10 to 17% of the amino acids have been modified in at least one IgE epitope so that IgE biding to the modified protein allergen is reduced as compared with IgE binding to the natural protein allergen, the at least one IgE epitope being one that is recognized when the natural protein allergen is contacted with serum IgE from an individual that is allergic to the natural protein allergen, (2) *any* modified protein allergen wherein about 10 to 17% of the amino acids have been modified in all the IgE epitope of the natural protein allergen, (3) *any* modified protein allergen wherein at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to any natural protein allergen, (4) *any* modified protein allergen wherein at least one modified amino acid is located within a central portion of the at lest one IgE epitope, the central portion including about 40% of the amino acids of the at least one IgE epitope, (5) *any* modified protein allergen wherein at least one amino acid in the at least one IgE epitope of any natural protein allergen has been modified by substitution, (6) *any* modified

protein allergen wherein at least one hydrophobic amino acid in the at least one IgE epitope of the natural protein allergen has been substituted by a neutral or hydrophilic amino acid, (7) *any* modified protein allergen retains the ability to activate T cells, (8) *any* modified protein allergen retains the ability to bind IgG, (9) *any* modified protein allergen retains the ability to initiate a Th1-type response, (10) *any* modified protein allergen is *any* portion of the natural protein allergen, (11) *any* combination of *any* modified protein allergen and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ, and immune stimulatory oligodeoxynucleotide sequence containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response, (12) *any* modified protein allergen is made in transgenic plant or animal, (13) *any* modified protein allergen expressed in a recombinant host selected from the group consisting of bacteria, yeast, fungi, and insect cells, (14) *any* modified protein allergen wherein the natural protein allergen is obtained from a source selected from the group consisting of legumes, milks, grains, eggs, fish, crustaceans, mollusks, insects, molds, dust, grasses, trees, weeds, mammals, and natural latexes, (15) *any* modified protein allergen made by the process of claim 53, (16) *any* combination comprising any natural protein allergen and any masking compound wherein the masking compound being covalently or non-covalently bound to at least one IgE epitope of any natural protein allergen in such as a way that IgE binding is reduced as compared with IgE binding to the natural protein allergen in the absence of the masking compound, wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen, (17) *any* combination wherein the at least one IgE epitope is one that is recognized when the natural protein allergen is contacted with a pool of sera IgE taken from a group of at least two individuals that are allergic to the natural protein allergen, (18) *any* combination wherein the masking compound is *any* antibody that binds non-covalently to the least one IgE epitope, (19) *any* combination retains the ability to activate T cells, (20) *any* combination retains the ability to bind IgG, and (21) any combination retains the ability to initiate a Th1-type response.

With the exception of modified allergens from peanut mentioned above, there is insufficient written description about the structure associated with functions of *any* modified protein allergen and *any* combination of *any* modified protein allergen.

Given the lack of a written description of any additional species of modified protein allergen and combination thereof, one of skill in the art would reasonably conclude that the

disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. Claims 37-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claims 37-59 as written represent a departure from the specification and the claims as originally filed.

The recitation of "whose amino acid sequence is substantially identical to that of a natural protein allergen except that about 10 to 17% of the amino acids have been modified in at least one IgE epitope" in claim 37 is not supported by the specification or by the claims as originally filed.

The recitation of "about 10 to 17% of the amino acids" in claim 38 is not supported by the specification or by the claims as originally filed.

The recitation of "at least one modified amino acid is located within a central portion of the at least one IgE epitope, the central portion including about 40% of the amino acids of the at least one IgE epitope" in claim 40 is not supported by the specification or by the claims as originally filed.

The recitation of "and immune stimulatory oligodeoxynucleotide sequence containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response" in claim 47 is not support by the specification or by the claims as originally filed. The specification and the claims as originally filed require that the adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and immune stimulatory sequences.

The recitation of "natural" in claims 37-39, 41-42, 46, 51-52 is not support by the specification or by the claims as originally filed.

The recitation of "In combination, a natural protein allergen and a masking compound, the masking compound being covalently or non-covalently bound to at least one IgE epitope of the natural protein allergen is such as a way that IgE binding is reduced as compared to the natural protein allergen in the absence of the masking compound wherein the at least one IgE

epitope is one that is recognized when the natural protein allergen is contacted with serum IgE in the absence of the masking compound, the serum IgE taken from an individual that is allergic to the natural protein allergen" is not support by the specification or by the claims as originally filed.

The recitation of "the masking compound is an antibody that binds non-covalently to the at least one IgE epitope" in claim 56 is not support by the specification or by the claims as originally filed. Thus the claimed invention constitutes **new matter.**

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 37-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "except that about 10 to 17% of the amino acids have been modified" is ambiguous and indefinite because it is unclear under which exception applicants intend to claim since the specification does not define the term. It is also not clear whether about 10 to17 % of the amino acids of the full length polypeptide or about 10 to17 % of the amino acids of the IgE epitope is being modified. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

The recitation of "In combination" in claims 47 and 54 is indefinite and ambiguous.

The recitation of "in such as way" in claim 54 is indefinite and ambiguous because it is not clear which way applicants intend to claim. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 37-46, 48-51 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,547,669 (Aug 1996, PTO 892).

The 5,547,669 patent teaches a modified protein allergen such as FEL DI from the cat which is a mammal, whose amino acid sequence is substantially identical to that of a natural protein allergen except that modified protein binding to IgE is reduced at least by about 75% (See column 3, lines 36-45, in particular). The reference modified protein allergen (recombitope peptide) is a portion of the native protein allergen from cat produced by amino acid substitution wherein the amino acid is substituted by neutral amino acid such as alanine (See column 15, lines 1-5, 15-17) or substituted with hydrophilic amino acid such as lysine (KK) and arginine (RR) (See column 15, lines 59-62, in particular) or produced recombinantly in host cell such as bacteria (E coli), wherein the modified protein allergen stimulates T cell activity such as T cell proliferation better than native protein allergen (See column 24, lines 8-67, bridging column 25, lines 1-32, in particular), the modified protein initiates delayed type sensitivity which is Th-1 response (See column 26, lines 60-62, in particular) and reduces IgE binding (See column 22, lines 44, column 23, lines 59-61, in particular). Claims 48-49 are included in this rejection because the claims recite a product by process. The recitation of a process limitation in claim 48-49 is not seen as further limiting the claimed product, since multiple processes can make equivalent products. Thus, the reference teachings anticipate the claimed invention. Claim 40 is included in this rejection because the recitation of about 40% of the amino acids of the at least one IgE epitope is an inherent property of the reference modified protein allergen since the reference allergen has reduced IgE binding. While the reference is silence that the reference modified protein allergen has the property of that recited in claim 44, the ability to bind IgG is the inherent property of the reference modified protein allergen. Therefore the claimed modified protein allergen appears to be the same as the modified protein allergen of the prior art in the absent of a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show an unobvious distinction between the antibodies of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The '669 patent further teaches a method for designing recombitope peptides of any allergen where the protein antigen to which the individual is senstive has unknown or ill-defined epitope (See abstract, in particular) and the modified protein allergen is useful for desensitize the

individual to the protein allergen (See column 3, lines 34-36, in particular). Thus, the reference teachings anticipate the claimed invention.

11. Claims 54-59 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No. 5,449,669 (Sept 1995, PTO 892).

The 5,449,669 patent teaches a method of determining the allergenic IgE binding of a natural protein allergen by means of placing a combination of synthetic polypeptide based on the natural protein allergen such as shrimp tropomyosin Pen i I and a masking compound wherein the masking compound is tropomyosin-specific IgE antibody being non-covalently bound to at least one of the IgE epitope of the native protein tropomyosin using sera of allergic patients and determining the inhibition of binding of tropomyosin-specific IgE antibodies to tropomyosin (See column 6, lines 32-68, column 7, lines 1-16, in particular). Claims 57-59 are included in this rejection because since the claimed protein allergen is a natural protein allergen, it is inherent that the natural protein has the ability to activate T cells, binds IgG and initiates a Th1-type response. Thus, the reference teachings anticipate the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 37 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Hoyne *et al* (of record, Immunology and Cell Biology 74: 180-186, 1996, PTO 892).

The teachings of the 5,547,669 patent have been discussed supra.

The claimed invention in claim 47differs only by the recitation of in combination of the modified allergen and an adjuvant selected from the group consisting of IL-12, IL-16, IL-18, IFNγ and immune stimulatory oligodeoxynucleotide sequences containing unmethylated CpG motifs which cause brisk activation and skew the immune response to a Th1-type response.

Hoyne *et al.* teach patients receiving the PLA-2 specific peptides from bee venom demonstrated a decrease in allergen specific IgE and a corresponding rise in IgG levels; most patients reported a significant improvement in clinical symptoms (See page 183, column 1, paragraph 2, in particular). Hoyne *et al.* further teach peptide-mediated regulation of allergic immune response and a successful desensitization using peptide-mediated immunotherapy is accompanied by a decrease Th2-type cytokine with a concomitant increase in IFNγ production (See page 180, column 2, in particular). The reference further teaches that the key to successful immunotherapy may dependent on reprogramming the immune response by co-administering modified allergen peptide in the presence of IL-12 or IFNγ (See page 183, column 2, paragraph 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate modified allergen in the presence of IL-12 or IFNγ because the key to a successful peptide-based immunotherapy depends on reprogramming the immune response by co-administering allergen peptide in the presence of IL-12 or IFNγ because IL-12 or IFNγ would down-regulate ongoing Th2 responses in vivo by suppressing IgE production as taught by Hoyne et al (See page 183, column 2, in particular).

15. Claims 37 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,547,669 (Aug 1996, PTO 892) in view of Burks *et al* (of record, J Allergy Clin Immunol 6-93(4): 743-50; 1994 PTO 1449).

The teachings of the 5,547,669 patent have been discussed supra.

The claimed invention in claim 52 differs only by the recitation of modified protein allergen is peanut protein selected from the group consisting of Ara h1, Ara h2 and Ara h3.

Burks *et al* teach a major allergen of peanuts such as Ara h1 and the IgE binding specificity of Ara h1 antibodies is determined by competition ELISA using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular). Burks et al further teach that the allergen is purified by affinity column chromatography and the Ara I allergen has a molecular weight of 63.5 kd and an isoelectric point of 4.55 while the second allergen such as Ara II has a molecule weight of 17 kd and an isoelectric point of 5.2(See Abstract, page 749, column 1, first full paragraph, in particular). The reference further teaches that peanuts are considered one of the most allergenic food (See page 743, column 1, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify at least one of the IgE binding epitope of Ara h1 or Ara h2 as taught by Burks by amino acid substitution as taught by '669 patent for a modified protein allergen wherein the IgE binding of the modified protein allergen is reduced for desensitization immune therapy. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Burks *et al* teach peanuts are considered one of the most allergenic food (See page 743, column 1, in particular) the IgE binding specificity of one of the major protein allergen of peanut Ara h1 antibodies is determined by competition ELISA using pooled peanut-specific IgE from patients allergic to the natural protein peanut allergen (See page 746, Table II, in particular). The '699 patent teaches that the modified the modified protein allergen is useful for desensitize the individual to the protein allergen (See column 3, lines 34-36, in particular).

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

19. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
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December 17, 2001

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